

EFPIA CDEG position paper on the use of Form FDA 1572 for clinical trials performed outside the USA

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The EFPIA Clinical Development Expert Group (CDEG) was made aware that some EU competent authorities (e.g. in Belgium, Germany, Denmark, Sweden, Norway) are refusing to allow investigators at sites in their country to sign Form FDA 1572 because they determined that by doing so, the investigator is agreeing to comply with all applicable U.S. regulatory provisions, which are not applicable in their country and conflict, with regard to a number of points, with observance of the national or EU law that applies for the Investigator. Also, a clinical trial cannot be conducted under any foreign country legislation and all trials must be conducted in accordance with the national legislation of the country in which the trial is carried out and ICH-GCP ensure a basic harmonization across borders. So as long as the sponsor and the investigator demonstrably comply with the national legal requirements and the GCP principles, there is no major shortcoming when comparing the different national requirements and therefore there is no need for signing the FDA Form 1572. **Several Member State authorities have therefore recommended that sites in their country should be classified as non-IND sites therefore not requiring the collection and signing of 1572 Forms for FDA purposes.**

In United States law, the “Form FDA 1572” is based on Title 21 Code of Federal Regulations (CFR) 312.53 (c) “Responsibilities of Sponsors and Investigators: Selecting Investigators and monitors” and **must be signed** by the Investigator only **if a clinical trial is to be conducted as an “IND study”** (Investigational New Drug Study).

Under item 9 on the form, “Commitments,” the following guidelines are among those which the Investigator, with his signature, agrees to observe:

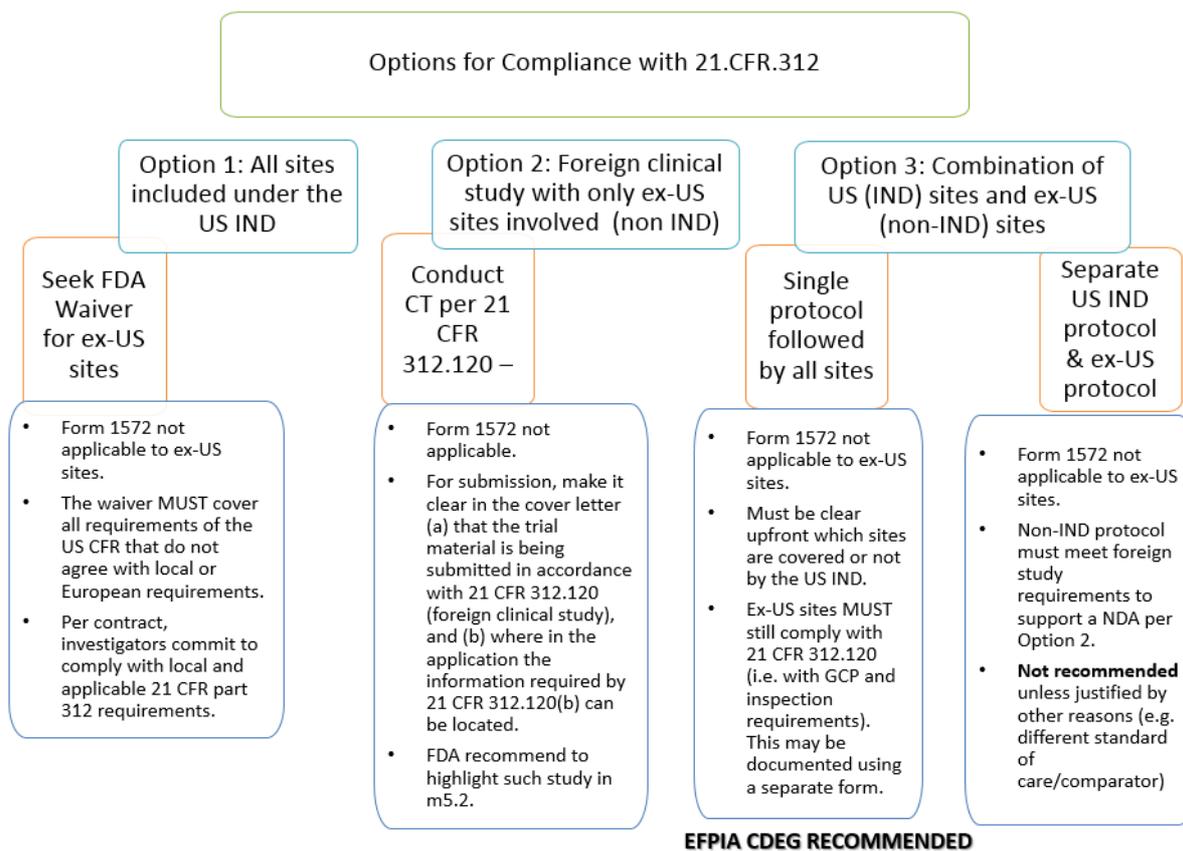
- Title 21 CFR Part 50 (obtaining informed consent)
- Title 21 CFR Part 56 (ensuring that an Institutional Review Board, which complies with the requirements of 21 CFR Part 56, will be responsible for review and approval)
- Title 21 Part 312 (compliance with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements)
- Title 21 CFR 312.62 (maintaining adequate and accurate records, making these records available for inspections in accordance with 21 CFR 312.68)
- Title 21 CFR 312.64 (reporting of adverse experiences that occur in the course of the investigation)

As these are U.S. regulations, which cannot be applicable outside the US and are not generally known and understood by investigators in the EU or outside US. Neither are ex-US investigators usually aware of any possible consequences of non-compliance with these provisions which may in addition contradict the legal requirements for clinical trials in their own country.

In addition, already for decades, a large degree of harmonization – both in ethical terms and also in the fundamental approaches in the planning and carrying out of investigations – is brought about by the internationally recognized standard for Good Clinical Practice (GCP) of the International Council

for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Against this background, the ICH GCP E6(R2) Guideline constitutes an important bridge between clinical investigations carried out in the USA, the EU and beyond.

As a result, in 2018/2019 the EFPIA CDEG conducted a survey amongst its member organizations to evaluate the potential impact of the non-acceptance of Form FDA 1572 ex-US by EU Member States. The outcome of this survey showed that standard practices regarding the use of Form FDA 1572 in the EU (or other countries outside US) is not consistent across companies and there seems to be a need to provide clarity and recommendations when the FDA form is rejected by EU national Health Authorities, which could cause undue delay in starting a clinical trial. Therefore, this position paper provides recommendations as to when a Form FDA 1572 should be used in a clinical trial and when it should not as illustrated in the diagram below, with additional details in the subsequent pages.



Clinical trials submitted to the US Food and Drug Administration (FDA) to support a marketing approval or an indication extension must comply with the IND regulations found in Title 21 Code of Federal Regulations (CFR) Part 312.

Compliance with 21 CFR 312 can be achieved:

- 1) By conducting trials under an IND
- 2) By conducting trials that are not part of an IND using sites located outside the US (non-IND foreign clinical studies) or
- 3) Conducting trials using a combination of sites located within the US (as IND-sites) and sites located outside the US that are not under the IND application (non-IND sites).

Three options have been identified, for which the pros & cons are detailed further below.

Option (1):

The sponsor chooses to submit a single protocol to the IND and conduct the trial for all trial sites (both in US and outside US) under IND, and the sponsor and **all investigators** must meet **all IND requirements** unless the sponsor requests FDA to grant a waiver of any applicable requirement in 21 CFR 312 for a specific trial site and FDA agrees to the waiver. The sponsor should submit the waiver request to the IND under which the study will be conducted, however it is understood such waiver requests should remain an exception as other options are available.

If the FDA grants a waiver at the sponsor's request:

- i. The sponsor must check that the waiver covers all requirements of the US CFR that do not agree with local or EU requirements, such as IRB requirements, reporting of safety data, data protection requirements, archiving periods, etc.
- ii. The Sponsor must elucidate/inform the trial sites outside the US about the requirements of the CFR, especially about all those requirements that conflict with or supplement the local or EU legal requirements. In the investigator contract it must be made clear that the investigator commits to comply with local legislation and requirements as well as the applicable regulations under 21 CFR Part 312.
- iii. Documentation of (i) and (ii) needs to be archived in the Investigator Site File (at the sites) and the Trial Master File.

Option (2):

The sponsor chooses to conduct a clinical trial outside an IND exclusively at sites located outside the US therefore there is no requirement for FDA Forms 1572 to be signed. If the trial results are to be used for a US submission, then the trial must be conducted in accordance with 21 CFR 312.120 – Foreign clinical studies not conducted under an IND.

“Under 21 CFR 312.120, FDA will accept a well-designed, well-conducted, non-IND foreign study as support for an IND or application for marketing approval if the study was conducted in accordance with GCP and if FDA is able to validate the data from the study through an onsite inspection, if necessary.”⁽²⁾

Marketing approval of a new drug based solely on foreign clinical data is governed by 21 CFR 314.106.

NB: If Option (2) is chosen, when submitting information about a non-IND foreign clinical trial it should be clearly identified in the cover letter (a) that the trial material is being submitted in accordance with 21 CFR 312.120, and (b) where in the application the information required by 21 CFR 312.120(b) can be located. Within an eCTD format, FDA recommends that a sponsor or applicant highlights the studies subject to the requirements of 21 CFR 312.120 in Section 5.2 of Module 5.

Option (3):

The sponsor chooses to conduct a multinational clinical trial with sites both inside and outside the US. In this case the sponsor can choose to exclude sites outside the US from the IND application (as non-IND sites) but to keep the US sites under the IND. There are then 2 potential sub-options:

- i. The sponsor can run the study under one protocol as long as it is clear to the FDA which sites are operating under the IND and which are not. The Form FDA 1572 does not apply for

non-US sites and concerned investigators at these non-IND sites do not have to sign the Form FDA 1572. However, the sponsor must ensure that the non-IND sites comply with 21 CFR 312.120 (i.e. with GCP and inspection requirements). Sponsors may choose to achieve this e. g. via a form and/or signed declaration by the trial sites to confirm their adherence to GCP in relation to items such as adequate medical qualification and training, collection of informed consent, review by IRB etc.

- ii. The sponsor can run the study under 2 separate protocols. The FDA guidance⁽¹⁾ provides an additional option for the sponsor to submit one protocol for sites under the IND and a separate protocol for foreign sites not under the IND. The Form FDA 1572 does not apply for non-US sites; however, the non-IND protocol would need to meet FDA requirements for acceptance of a 'foreign' study (21 CFR 312.120 and 314.106) in order to support a US application. Therefore, unless there are additional reasons (beyond FDA 1572 compliance) to have separate protocols for IND and non-IND sites (e.g. different standard of care or comparator arm), the additional effort of maintaining separate protocols may not be justified.

EFPIA recommendation: Option (3i)

- Sponsors are recommended to incorporate sites located outside the US as non-IND sites in the clinical trial. As long as these sites meet the requirements of 21 CFR 312.120 this is acceptable for the FDA and avoids the need for concerned investigators to sign Form FDA 1572. So, if the sponsor and the investigator demonstrably comply with the national legal requirements and the GCP principles and this is documented, there is no major shortcoming when comparing and applying the different national and GCP requirements. There is precedent in such an approach in many companies.
- When conducting a multinational clinical trial (with sites in US and outside US) it should be the company's decision to assess and decide whether to use a single protocol (recommended) or a separate protocol for the non-US sites (that are not under the IND).
- In any case, it is recommended to discuss plans on how to pool data from separate IND / non-IND protocols with the FDA prior to starting the trial.

References:

- 1) Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs, Frequently asked Questions – Statement of Investigator (Form FDA 1572), May 2010;
<https://www.fda.gov/media/78830/download>
- 2) Guidance for Industry and FDA Staff: FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND - Frequently Asked Questions <https://www.fda.gov/media/83209/download>